Original Article
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Electrophysiology of Human Gametes: A Systematic Review

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Purpose: Oocytes and spermatozoa are electrogenic cells with the ability to respond to electrical stimuli and modulate their electrical properties accordingly. Determination of the ionic events during the gamete maturation helps to design suitable culture media for gametes in assisted reproductive technology (ART). The present systematic review focuses on the electrophysiology of human gametes during different stages of maturation and also during fertilization.
Materials and Methods: The reports published in the English language between January 2000 and July 2021 were extracted from various electronic scientific databases following the PRISMA checklist using specific MeSH keywords.
Results: Subsequent to the screening process with defined inclusion and exclusion criteria, 60 articles have been included in this review. Among them, 11 articles were directly related to the electrophysiology of human oocytes and 49 physiology department to the electrophysiology of human spermatozoa.
Conclusions: Gametes generate electrical currents by ionic exchange, particularly Na^+, K^+, Cl^-, H^+, Zn^{2+}, Cu^{2+}, Se^{2+}, Mg^{2+}, HCO_3^-, and Ca^{2+} through specific ion channels in different stages of gamete maturation. The ionic concentrations, pH, and other physicochemical variables are modulated during the gametogenesis, maturation, activation, and the fertilization process following gamete function and metabolism. The electrical properties of human gametes change during different stages of maturation. Although it is demonstrated that the electrical properties are significant regulators of cell signaling and are fundamental to gamete maturation and fertilization, their exact roles in these processes are still poorly understood. Further research is required to unveil the intricate electrophysiological processes of human gamete maturation.

Keywords: Electrophysiology; Fertilization; Ion exchange; Oocyte; Sperm maturation and ovum instead; Spermatozoa

INTRODUCTION

The growth and differentiation of germinal cells follow distinct rhythms of long-term quiescent states. The electrical changes caused by the alterations in specific ionic concentrations across the mitochondrial and/or plasma membrane (PM) of gametes are necessary for cellular activity and vitality [1]. The presence of different electrical charges between the interior and exterior of the membrane causes an electrical gradient across

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a gamete [1]. The resting membrane potential (RMP) ranges from -75 mV to -35 mV for human spermatozoa in different maturation stages. Non-capacitated and capacitated sperms exhibit RMP of around -40 mV and -58 mV, respectively [2].

The RMP of fertile mammalian oocytes ranges from -19 to -51 mV, a value that varies depending on the developmental stage, species, strain, and also on extracellular environment in different media [1]. Germinal vesicle (GV), metaphase I (MI), metaphase II (MII), two-pronuclei oocytes, two-cell, and four-cell embryos, respectively exhibit RMP of around -31, -34, -32, -30, -30, and -29 mV [1]. Electrical changes regulated by the controlled ionic currents through channels and transporters affect the maturation and fertilization of gametes. Therefore, the electrophysiological studies on human gametes and ion channels in the different stages of maturation and also during fertilization may be of particular importance in elucidating the electrophysiological mechanisms that lead to infertility in humans. Moreover, it is also critical to design suitable culture media and improve the quality of currently used culture media for gamete and embryo for a better outcome in assisted reproductive technology (ART). The present systematic review aims to collate the relevant published reports on the electrophysiology of human gametes as well as to concisely provide an understanding of the role of ionic currents in regulating various functions of the gametes.

MATERIALS AND METHODS

The present systematic review includes reports on human gametes' electrophysiology published in the English language between January 2000 and July 2021, extracted from various electronic databases such as PubMed, Scopus, Science Direct, and Google Scholar following the PRISMA checklist. The MeSH terms used were "electrophysiology OR ion channel" AND "oocyte AND/OR spermatozoa". Following the exclusion of non-English and review articles, potential articles were screened by title, abstract, and full text. Both *in vitro* and *in vivo* studies that met our inclusion criteria were included in this article. Studies were analyzed individually by two of the authors, any disagreements were solved by consultation with other authors.

RESULTS

A total of 34,168 articles were included to this study through electronic database. Among these articles, 20,723 were non-English language and not relevant to human, 12,553 were older than 20 years, 552 were review articles and original studies not reporting gamete channels. During the final screening, gray literature, including unpublished research, theses, conference pre-

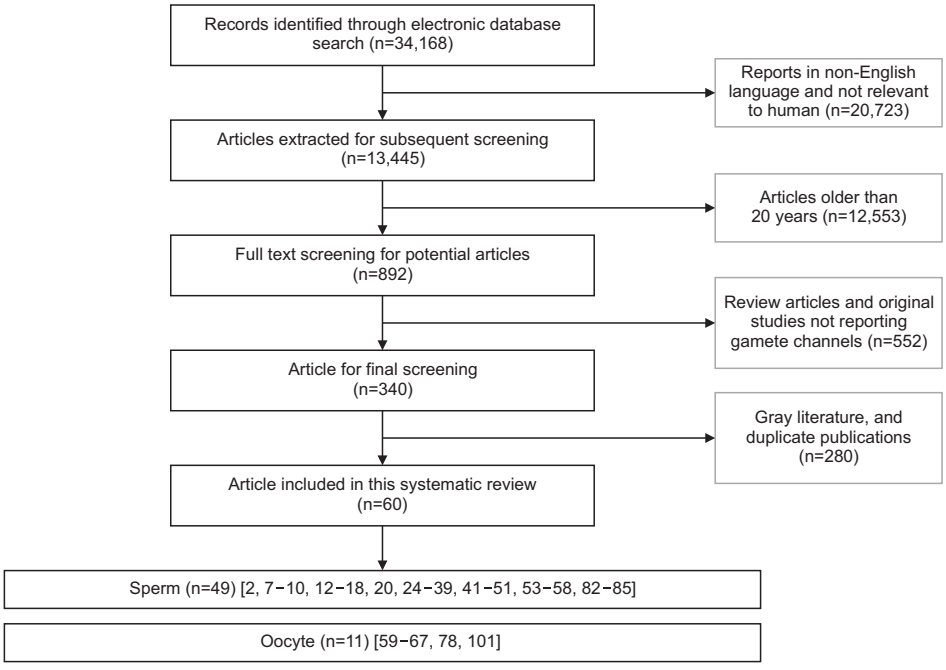

Fig. 1. PRISMA flowchart for literature screening.

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sentations, and duplicate publications were excluded from our study (n=280). Obtained data were then cross-checked, and articles focused on the electrophysiology of human oocyte and/or spermatozoa were included in the study (n=60) (Fig. 1).

DISCUSSION

1. Electrophysiology of spermatozoa

1) Ion channels regulating spermatogenesis and sperm maturation

Several ion currents participating in spermatogenesis and spermiogenesis have been reported (Table 1, Fig. 2) [3-5]. At the beginning of spermatogenesis, the stem cell niche, as a microenvironment, supports and regulates spermatogonial stem cells through cell-cell interactions, extracellular communication, and matrix components (such as pH, ionic concentration, and other existing factors) [3-5]. Sertoli cells in the epithelium of the seminiferous tubules play an important role in the development of germ cells by controlling the the matrix contents and providing structural and nutritional support [3-5]. This support provides the passage of non-motile spermatozoa from testes into the efferent duct [3-5]. The movement of H_2O, Na^+, Cl^-, HCO_3^-, and K^+ have been reported in the Sertoli cell PM [3-5]. These ions transfer through aquaporin (AQP), various membrane pumps, and ion channels that present and support ion composition, osmolarity, and pH of the fluid by secretion and absorption during spermatogenesis [3-5]. These concentrations differ across the seminiferous epithelium related to the germ cells' morphological and volume changes [3-5]. These ion exchangers in Sertoli cell are Na^+/K^+ exchanger (NKX), PM Ca^{2+}-ATPase (PMCA) and a probable V-type ATPase, Na^+-dependent Cl^-/HCO_3^- exchangers, Na^+/HCO_3^- cotransporters, Na^+/H^+ exchanger (NHX), Na^+-K^+-$2Cl^-$ cotransporter (NKCC) and Na^+/Ca^{2+} exchanger (NCX). Also, the related ion channels are included voltage-gated Cl^- channels (CLC) activated by acidic pH, cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channels, K^+ channels, and L-T-and N-type voltage-gated Ca^{2+} channels (VGCC) [3-5]. Leydig cells, a type of interstitial cells, are the site of steroidogenesis and testosterone synthesis in the testis [6]. It has been shown that Zn^{2+} deficiencies lead to a decline in testosterone production and disrupt spermatogenesis [6]. In the spermiogenesis process,

Table 1. Ion channels, their distribution, and functions in oocyte and sperm membranes

Ions	Some vital oocyte ion channels	Functions	Some vital spermatozoa ion channels	Functions
K^+	K_{ATP}	It has been reported in RMP [60,79], passing from the stage of GVBD and maturation [60,79] and fertilization [60], activation of oocytes [60].	KV, SLO, KSper, KCa, Na^+-K^+-ATPase, K_{ATP}	It has been reported in hyperpolarization/depolarization [2,14,16,32, 44-47,50,51], opening the VGCC [2,44,45], maturation [15], motility [14,37-39], sperm volume regulation and adaptation [13,15-17], capacitation and hyperactivation [2,14,15,32,44,46,47,84], AR and fertilization [14,17,44,45,84].
Na^+	NHX, NKX, Na^+/NH_4^+ exchanger, Na^+/HCO_3^- exchanger, NaV, NCX, nonselective cation channel	It has not been reported in the human oocyte, but it has been seen in mammalian passing from the stage of GVBD, maturation, and size regulation of pre-implantation embryos [67,74].	NHX, NaV, NCX, Na^+-K^+-ATPase	It has been reported in hyperpolarization/depolarization [50,51], opening the voltage-dependent Ca^{2+} channels [50], motility [29,37-39], maturation [36], capacitation [50,53], and fertilization [29,36,53].
H^+	H^+ pump	It has been reported in MMP [64,65], intracellular signaling [64,65], maturation [64,65,67], fertilization [64,65], embryo development [64,65].	CHX, HV, NHX, HSper	It has been reported in hyperpolarization/depolarization [32], pH [35], voltage dependent gating [35,84], maturation [25-28], motility [7,14,25-28], AR and fertilization [7,25-28,84] and MMP [25-28].

Table 1. Continued

Ions	Some vital oocyte ion channels	Functions	Some vital spermatozoa ion channels	Functions
Ca^{2+}	CX43, CX26, IP3, TRP channel	It has been reported in passing from the stage of GVBD and maturation [59,61-63,66], quality [66], fertilization [61-63].	VGCC, PMCA, CHX, CatSper1-4, receptor-operated Ca^{+} channel, NCX, STIM-ORAI, TRP channel	It has been reported in hyperpolarization [9,32,34,44,47,50,51,57,85,86], maturation [7,9,10,29,35,36], motility [7,14,20,29,33,35,37,38,42,48], capacitation and hyperactivation [20,32,33,36-38,41,42,44,47-49,84], AR and fertilization [7,20,30,31,33-38,42,44,48,56,83,84].
Cl^{-}	HCO_3^{-}/Cl^{-} exchanger, Cl^{-}/OH^{-} exchanger, CaCC, CLC, GABA	It has not been reported in the human oocyte, but it has been seen in mammalian for passing from the stage of GVBD, maturation, embryo development [75], and size regulation.	CaCC, CLC, VGIC, Na^{+}-dependent Cl^{-}/HCO_{3-} exchanger, NKCC, GABA, CFTR	It has been reported in maturation [7,15], sperm physiology and function [8], sperm volume regulation [13,15], effect on the RMP [8,52], hyperactivation, capacitation [15,52-54], AR and fertilization [31,52-54,58].
HCO_3^{-}	Na^{+}/HCO_3^{-} exchanger, HCO_3^{-}/Cl^{-} exchanger	It has not been reported in the human oocyte, but it has been seen in mammalian in maturation [74], embryo development [74].	VGIC, Na^{+}-dependent Cl^{-}/HCO_{3-} exchanger, CFTR	It has been reported in capacitation [52-54], signaling pathway [41].
Mg^{2+}	VGIC	It has a role in the improvement of the oocyte-to-embryo transition and the blastocyst development [87].		
Mn^{2+}	VGIC	It is negatively associated with oocyte maturation [72].	VGIC	It participates in spermatogenesis in mammals [23].
Cu^{2+}	VGIC	It has been related to lower embryo fragmentation [72] and higher pronuclear formation in mammals [40].	VGIC	It can enhance sperm motility, viability, functional membrane integrity, and zona binding in mammals [40]. On the other hand, in humans, it has an inverse effect on sperm concentration [24].
Zn^{2+}	VGIC	It has a role in regulating and completing of meiosis, egg activation, and the terminal stage of oocyte development in mammals [70] and oocyte fertilizability in humans [72].	VGIC	It participates in anatomical development [7], ribonuclease activity in the initiation of spermatogenesis during the mitosis of spermatogonia, and meiosis of spermatocytes [7,11,90], the maintenance of germ cells and seminiferous tubule during spermatogenesis [7,11,90]. It also affects Ca^{2+} influx through VGCC [7].
Cr^{2+}	VGIC	It is negatively associated with oocyte maturation [72].		
Se^{2+}	-	In mammals, it improves oocyte maturation, fertilization, and blastocyst development [88].	VGIC	It has protective antioxidant properties and has a role in spermatogenesis, formation of sperm midpiece and flagella, sperm quality, sperm motility, mitochondrial morphology, and function [91].
Ni^{2+}	-	In frog, a deficient concentration of Ni^{2+} can lead to a hormonal sensitivity and maturation activity of oocyte [89], but it has not been reported in mammals and human.	VGIC	It has a role in spermatogenesis [22] and influences the functions of CNG channels in mammals [22].

RMP: resting membrane potential, GVBD: germinal vesicle breakdown, AR: acrosome reaction, MMP: mitochondrial membrane potential, RMP: resting membrane potential, VGCC: voltage-gated Ca^{2+} channel, CNG: cyclic nucleotide-gated, -: not available.

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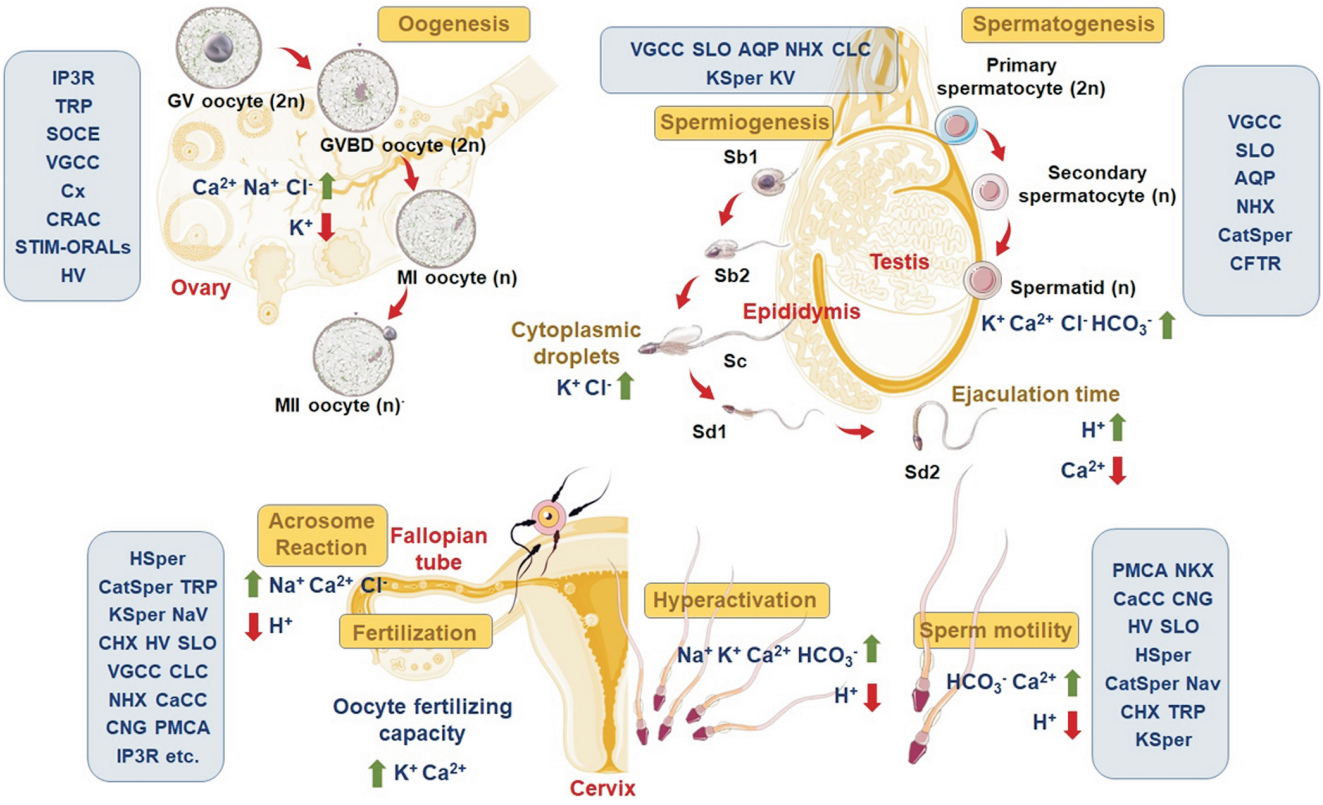

Fig. 2. Channels and ions involved in gamete developmental and maturational stages. AQP: aquaporin, CaCC: Ca^{2+}-activated Cl- channels, CHX: Ca^{2+}/H^+ exchanger, CRAC: Ca^{2+} release-activated Ca^{2+} channels, HSper: H^+ channel of sperm, NKX: Na^+/K^+ exchanger, CatSper: sperm cation channel, KSper: sperm K^+ channel, SLO: sperm specific K^+ channel, SOCE: store-operated Ca^{2+} entry, STIM-ORAI: store-operated ORAI calcium channels, TRP: transient receptor potential channel, VGCC: Voltage-gated Ca^{2+} channel, HV: voltage-gated H^+ channel, KV: voltage-gated K^+ channels, NaV: voltage-gated Na^+ channel.

spermatids acquire elongated shape with distinct tail, midpiece, their PM's physiological status changes, and gain a certain degree of motility [7,8].

Studies have demonstrated that K^+, Na^+, Ca^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+}, Se^{2+}, Mg^{2+}, H^+, and Cl^- ions may have an important role in spermatid differentiation [7,8]. In mammals, Zn^{2+} is involved in the anatomical development and normal functions of male reproductive organs. It has a role in ribonuclease activity in spermatogenesis initiation, during the mitosis of spermatogonia and meiosis of spermatocytes [7]. It also participates in germ cell functions during spermatogenesis [7], spermatozoa maturation and motility [7]. Besides, VGCC are transmembrane proteins that are classified into two groups: low-voltage activated (LVA or T-type) and high-voltage activated (HVA or L-, N-, P/Q- and R-type) channels, which play important roles in Ca^{2+} flux in immature spermatogenic cells and mature spermatozoa after the transfer of ion channels to planar lipid bilayers [9-11]. Zn^{2+} negatively regulates the VGCC channel in human spermatozoa [7]. K^+ current through some K^+ channels, including the acid-sensitive and voltage-gated types, was suggested to play the human spermatozoa volume regulation [12,13]. Sperm-specific K^+ channel (SLO_3) as a high-conductance K^+ channel is expressed in human testes and involved in various male fertility mechanisms [14]. In human spermatozoa, the osmotic concentration and sperm volume adaptation are expressed by the cytoplasmic droplet (CD), and the regulatory volume decrease (RVD). RVD discusses the loss of CD, and both of them are related to the function of K^+ and Cl^- channels, AQP around the spermatozoa midpiece membranes, sperm swelling at ejaculation, and consequences for fertility [13,15-17]. The AQP has been detected in the human testis, specifically in the tail of spermatid and spermatozoa and has a role in sperm motility [3,18]. This process may be accompanied by Na^+ and H^+ ion currents through NHX in which internal H^+ is exchanged for external Na^+ ions. This raises intracellular pH (pHi), activates axonemal sliding (that remains inhibited in low pH), and activates K^+ channels that are responsible for hyperactivation [19]. This

process involves the response development to Ca^{2+} and cyclic AMP and downstream signaling systems [19]. Moreover, PMCAs facilitate a higher Ca^{2+} turnover in sperm necessary to traverse the female reproductive tract (FRT) [20]. Studies showed that before ejaculation, spermatozoa are stored in the epididymis fluid where the osmolality and K^+ gradient are high and ionic strength, Na^+, and pH are low [19]. At the moment of ejaculation, spermatozoa are in a reversal situation where osmolality and K^+ are low and ionic strength and Na^+ are high and additional components from the accessory sex glands are added too [19]. Hence, at ejaculation, spermatozoa are abruptly facing a severe decrease in osmolality [19]. In mammals, some trace metals like Se^{2+} [21], Ni^{2+} [22], and Mn^{2+} play minor roles in spermatogenesis [23]. In this context, Se^{2+} has protective antioxidant properties and participates in the processes of spermatogenesis, the formation of sperm midpiece and flagella, apoptosis, modification of cell signaling systems, and activation of transcription factors [21]. Ni^{2+} influences the functions of cyclic nucleotide-gated (CNG) channels [22] and Mn^{2+} accelerates spermatogenesis [23]. In human seminal plasma (SP), the Cu^{2+} level has been reported to have an inverse correlation with sperm concentration [24].

2) Ion channels regulating sperm functions

Several studies proposed that the functional integrity of sperm mitochondria and mitochondrial membrane potential (MMP) maintain sperm motility, normal morphology, quality, acrosome reaction (AR), and fertilizing potential [25-28]. Regulation of ionic currents like K^+, Na^+, Ca^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+}, Se^{2+}, H^+, Mg^{2+}, and Cl^- have been suggested to be involved in sperm functionality and progressive motility through the sperm cation channel (CatSper), voltage-gated ion channels (VGICs) such as proton (HV1), potassium (SLO3/KCNU1), sodium channels (NaV1.1-1.9), Ca^{2+}-activated Cl^- channels (CaCC), CNG and the transient receptor potential (TRP) channel family [29-31]. Se^{2+} is an essential trace element in the regulation of sperm quality and male fertility through cooperation with two selenoproteins containing phospholipid hydroperoxide glutathione peroxidase (PHGPx/GPx4) and selenoprotein P [21]. PHGPx/GPx4 is expressed in the testis germ cells' mitochondria and the midpiece of human spermatozoa [21]. Studies showed that spermatozoa's reduced expression of mitochondrial PHGPx might affect sperm motility, mitochondrial morphology, and sperm functions in men [21]. Sperm motility is fueled by hydrolysis of ATP by dynein resulting in axonemal bending, a process that involves pHi decrease via Ca^{2+}/H^+ exchange (CHX) and glycolysis [7,14]. Besides, many of the TRP channels, including TRPM8, TRPV4, TRPC1-C4, and TRPC6, are a superfamily of cation channels essential for human sperm motility [32-34]. The HSper channel (H^+ channel of sperm) transports H^+, exhibits extreme sensitivity to Zn^{2+}, and simulates the HV1 channel in human sperm [7,35]. Although HV1 is not an ion channel, it provides a voltage-gated mechanism through the transporter and ion channel to pass the H^+ across a lipid bilayer without the pore [7,32,35,36]. In ejaculation, SP contains two mM zinc, which directly inhibits the HV1 function [7]. It has been reported that sperm PMCA transporter, specially PMCA4 leads to motility, capacitation, and the AR probably through interaction with the NOSs at high cytosolic Ca^{2+} level and prohibiting raised levels of NO and apoptosis [20,37,38]. It has been shown that the Na^+-K^+-ATPases are essential in the regulation of sperm motility and are critical for sperm function [37-39]. Moreover, the addition of Cu^{2+} to the IVF medium enhances sperm motility and viability in mammals [40].

3) Ion channels regulating fertilization

After the irreversible sperm-oocyte binding, AR occurs, and the acrosome contents are released to digest the cumulus cells (CCs) and zona pellucida (ZP) [41]. Hyperactivation of sperm and its transport through the FRT are influenced by ionic or osmotic changes [41]. Intracellular Ca^{2+} is important for flagellar motility in hyperactivation and fusion of the acrosomal vesicle in AR [33,42]. The spermatozoa swimming behavior is controlled by increasing Ca^{2+} through Ca^{2+} sensing proteins (calaxins) and inhibition of dynein motors, commonly referred to as hyperactivation [33,42]. Through the sperm transport within the FRT, Zn^{2+} chelation performs using oviduct fluid proteins, and the HV1 channel gradually activates which commonly occurred during hyperactivation [7]. As mentioned, Ca^{2+} acts directly on the flagellum axoneme and is an essential regulative factor for sperm motility and hyperactivation [33,42,43]. In this process, CatSper1-4 and VGCC, type Cav2.3 in the principal piece of the sperm tail, are necessary for hyperactivated motility and male fertility [36]. Besides, VGCC, type Cav2.3 localized in

the acrosome area, induces Ca^{2+} influx and receptor-operated Ca^{2+} channel (ROCC, type IP3 receptors [IP3R]) localized acrosomal membrane of the sperm head and neck, takes out Ca^{2+} from the redundant nuclear envelope [7,33,35]. Although, Ca^{2+} influx through VGCC needs activation by Zn^{2+} efflux [7]. Studies showed that K^+ channels functionally exist in sperm cells and facilitate depolarizing spermatozoa and opening the VGCC [2,13,32,44-47]. The latest reports indicated a probable functional association between CatSper, SLO_3, HV1, and TRP channel family members as capacitive Ca^{2+} channels in human sperms [32,33,48,49]. The SLO_3, recognized as the key K^+ channel in sperm, is Ca^{2+}-independent and voltage/pH-sensitive, but it has been suggested that human capacitated spermatozoa have a modified version of SLO_3, which is Ca^{2+}-dependent and weakly pH-sensitive [2,46,47]. Sperm K^+ channel (KSper) is pH-insensitive and Ca^{2+}-dependent and could be inhibited by progesterone [14,36,47], and it seems that human KSper is simulated to the SLO_1 [14,36,47]. The low Na^+ concentration, acidic pHi, and Ca^{2+} decrease in epididymal fluids can open Ca^{2+} channels and occur capacitation [32,50]. So that, in low concentration of extracellular Ca^{2+}, a Ca^{2+} channel that plays a role in resting intracellular Ca^{2+} levels let Na^+ influence, creating depolarization and a significant Na^+ increase [50,51]. Following that, the Na^+/K^+-ATPase is stimulated, contributes to the sperm hyperpolarization [50,51]. During sperm capacitation and hyperactivation, the K^+ channel induces membrane hyperpolarization [2,32,45], and Ca^{2+} as well as Cl^- and HCO_3^- can modulate several protein phosphorylations [2,32,52]. The sperm CFTR has a role in the transport of Cl^- and HCO_3^- for sperm capacitation [53,54]. Modulation of extracellular pH linearly affects pHi, which increases during capacitation essentially over Cl^-, Na^+, and HCO_3^- reliant mechanisms [53,54]. In this way, pHi can influence sperm Ca^{2+} permeability, and acidic pHi maintains Ca^{2+} low in sperm [55]. So sperm cell requires Ca^{2+} and H^+ current for initiation of the AR [42,44,55,56], while K^+ current contributes to the hyperpolarization and regulation of sperm fertilizing capacity [7,44,50,51]. In the human sperm AR, the depletion of Ca^{2+} supplies can activate KSper channels' opening with K^+ current what causes the hyperpolarization, and the opening of VGCC with a consequent PM depolarization, which causes the capacitation [44,57]. TRP channels family is critical for AR and fertilization in human spermatozoa [32,33]. Also, several small peptides and glycoproteins on the oocyte's surface as a second messenger can stimulate sperm ion currents [33,42]. The K^+ current makes a sequential cascade of electrical events that contain hyperpolarization of the RMP, NHX, increasing pH, depolarization of RMP, effluxion of Ca^{2+}, and increasing cAMP [2,15]. It may be suggested that Na^+, Ca^{2+}, H^+, and K^+ currents are influenced by modification of RMP, increase in pH because of membrane pumps and transporters like NHX or a Na^+-dependent Cl^-/HCO_3^- exchanger and increase in the intracellular Ca^{2+} [7,52]. The NHX and pH increasing are stimulated by the recruitment of K^+ channels, resulting in a rapid transient hyperpolarization after depolarization mediated by Ca^{2+} [44]. Electrophysiological studies showed that the modulation in the Cl^- levels through various Cl^- channel types (like NKCC, CaCCs, GABA) on the sperm head take part in the AR induced by the ZP in humans [31,58]. Also, it has been reported that the addition of Cu^{2+} to the IVF medium enhances sperm functional membrane integrity and zona binding in mammals [40].

2. Electrophysiology of the oocyte

1) Ion channels regulating oocyte maturation

Ion channels such as that of K^+, Na^+, Ca^{2+}, Zn^{2+}, K^+, Cl^-, H^+, and Mg^{2+} are localized on the PM of oocytes, and mediates oocyte maturation and fertilization [1,59-67]. Transport of Ca^{2+} through ion channels is a critical for human oocyte maturation and fertilization [61,63]. For increasing the cell Ca^{2+} signal, Ca^{2+} ions are released into the cytoplasm both from the extracellular space or from the endoplasmic reticulum (ER). The oocyte ER usually has non-selective cation channels, like IP3R [61]. Some Ca^{2+}/permeable ion channels commonly detected in oocytes are TRP channels, store-operated Ca^{2+} entry (SOCE), and VGCC, which control multiple Ca^{2+}/dependent ion channels in the oocyte membrane [1,62,68].

It seems that, in mammalian oocytes, the Ca^{2+} influx pathway affects mostly through the SOCE that directly regulates Ca^{2+} concentration in intracellular ER supplies [1,68]. The ORAIs and Ca^{2+} release-activated Ca^{2+} channels (CRAC) are also two other transport types that produce highly Ca^{2+}-selective channels in the mammalian oocyte [68]. It is shown that, in mammalian oocyte maturation, the SOCE downregulation is mostly because of the ORAI1 internalizing and stromal

interaction molecule (STIM) restructuring [68]. The SOCE can be proceeded by communication between STIM1 and the TRP channel family [68]. In human and mammalian mature oocytes, the TRP channel as a cationic non-selective channel is controlled by common second messengers like PIP2 and intracellular Ca^{2+} [61,63] and gets activated by certain stimuli like changes in pH, temperature, and osmolarity [62]. Calcium channels mediate Ca^{2+} entrance and support Ca^{2+} influx during the GV breakdown (GVBD) and oocyte maturation [66]. Although not in human gametes, the presumable role of PMCA in mammalian oocyte maturation has been identified along with the requisite process for early embryogenesis [69]. Zinc is an important ion for the regulation and completion of meiosis, terminal stage oocyte development, and its activation [70,71]. In humans, the number of mature oocytes showed a negative association with the concentration of Cr^{2+} and Mn^{2+} in follicular fluid [72]. Some studies suggested that the mammalian oocyte membrane is permeable to Na^+, Cl^-, and K^+ (Table 1) [73-75] towing to the presence of Ca^{2+}/dependent Cl^-, K^+, Na^+, and non-selective cation channels [74]. In human oocyte, potassium channels such as K_{ATP} [60], voltage-gated K^+ channels (KV), and Ca^{2+} activated K^+ channels (KCa) have been confirmed, but their molecular characteristics in humans are yet to be revealed [67]. Fertilization in mammalian oocytes is noticeable by hyperpolarization, which seems to be done with KCa and K_{ATP} channels [60]. Chloride channels like swell-activated Cl^- channels, Ca^{2+}-activated Cl^- channels (CaCC), HCO_3^-/Cl^- exchanger, and transporters have been demonstrated in some mammalian oocytes that take a role in oocyte maturation and size regulation [74]. It was suggested that passing from the GVBD stage and oocyte maturation specifically needs a reduction in K^+ concentration. This is because of nullifying the K^+ and Cl^- voltage-gated currents and replacing them with Na^+ current [60]. Although investigators have shown that in some mammallian MII oocytes, HCO_3^-/Cl^- and NHXs are inactivated to downregulate the Na^+- and Cl^--dependent cell volume regulation [74,76]. Some studies have confirmed an existence of a voltage-gated H^+ current in human oocytes that any modifications in it are associated with the oocyte's membrane capacitance, the progress of meiotic maturation, and the readiness of the oocyte for fertilization [67,77]. In humans, there is close communication between immature oocytes and CCs by intercellular connections like gap junctions (GJs), which break down automatically in the maturation process [59,66]. GJ is a large intercellular channel structured as hexameric assemblies (connexons) with a combination of Connexin (Cx), which is associated with the cytoplasm of adjacent cells and lets the interchange of nutrients, metabolites, and signaling molecules [59,66]. It has been indicated that signals, including Ca^{2+} and cAMP through passing from the oocyte-CCs GJs, regulate oocytes maturation [59,66]. It has been shown that Cx_{26} has a role in the continuation of meiosis and promoting the GV stage to mature oocytes in humans [59]. It is well known that the mammalian oocyte PM is mainly penetrable to K^+, Cl^-, and partly to Na^+ and also has the $K_{ATP,}$ Na^+/H^+, Na^+/NH_4^+, Na^+/HCO_3^-, Cl^-/HCO_3^-, Cl^-/OH^-, H^+/organic cation$^+$, Na^+/K^+, K^+/Mg^{2+} exchanges, and Cl^- unidirectional flux activities which have not still reported in human oocytes [60,67,78]. Studies on oocytes showed that hyperpolarized RMP in meiotic arrest and depolarized RMP in withdrawal from the arrested state occur by the actions of gonadotropins on the CCs. Mitochondrial outer and inner membranes have a wide variety of ion channels, which create MMP [79,80]. In the outer membrane of mitochondria, the VGIC is in its open mode, is an anion-selective channel that also allows ATP, ADP, Pi, and cations (Ca^{2+}, K^+, and Na^+) to pass through CaCC, KATP, and NaV [80]. The "redox-driven proton pump" and "Proton leak" are two channels to control respiration and net H^+ transport in mitochondria [79,81]. The selective and nonselective ion channels are present in the inner membrane [79]. Mitochondrial Ca^{2+} uniporter (MCU), mitochondrial ATP sensitive K^+ channel (mitoKATP), K^+/Ca^{2+} channel (mitoKCa), inner membrane anion channel (IMAC), the Na^+/Ca^{2+} (mNCX) and zCa^{2+} (mHCX) exchanger channels are other inner membrane ion channels allowancing the passing of Ca^{2+}, K^+, Na^+ and regulating of PHi [79,81]. To act as the main elements of cell life and death, these channels might be activated under physiological and pathophysiological disorders [79]. In human oocytes, mitochondria play an important role in Ca^{2+} signaling by VGCC, mNCX and mHCX, PMCA, MCU, and mitoKCa channels [64,65]. VGIC has a large variability in the MMP value of mitochondrial membranes and has been considered a critical parameter for assessing oocyte quality and maturation [64,65].

2) Ion channels regulating fertilization

In the fertilization process, the activation signal is transmitted from the region of sperm entrance to the whole oocyte by increases in intracellular Ca^{2+}, which rapidly returned to baseline [82]. The exterior concentration of Ca^{2+} and the Ca^{2+} influx are critical for keeping oscillations caused by sperm [1,82]. These electrical currents on the PM of mammalian oocytes are mostly because of both L-type and T-type VGCC and voltage-independent Ca^{2+} channels, which release IP3-dependent Ca^{2+} [1]. Also, it has been reported that in the mammalian oocyte, Ca_V 3.2 T-type of VGCC channel contributes to filling the intracellular ER Ca^{2+} stores and preserves Ca^{2+} homeostasis for fertilization [1,83]. The first identified oocyte stimulator is sperm-induced Ca^{2+} release. The primary Ca^{2+} release induces opening of K^+/Ca^{2+} channel and aseries of hyperpolarizations occur following fertilization, but during this phase, there are no apparent changes in pH is observed [33,45,57,77,84,85]. Although the significant role of extracellular Ca^{2+} is still not exactly known, it is indicated that intracellular Ca^{2+} aided the opening of the Cl^- [36,52]. In the mammalian MII oocyte, Store-operated ORAI calcium channels (STIM-ORAI channels) are activated by depletion of Ca^{2+} from intracellular ER stores via STIM proteins (STIM1 and 2) in the fertilization process [68]. STIM protein is a Ca^{2+} sensor that activates the ORAI channels instead of effectors continuing the Ca^{2+} signal [68]. It is demonstrated that STIM1 co-localizing with an ER marker (ORAI1) forms distinct areas before fertilization in MII oocyte and early embryo development [68]. It is demonstrated that the PM of human oocytes or embryosare highly permeable to H^+ ions and are distributed evenly across the PM [77]. Thus an extracellular pH of about 7.5 is critical for their development [77]. Also, investigators have shown that in human oocytes, MMP is a critical parameter for evaluating oocyte fertilization, implantation, and embryo development [64,65]. The Cx_{43} level is also positively correlated with embryo quality, cleavage rate, and morphology [66], and low Mg^{2+} concentration in the IVF medium lead to improved oocyte-to-embryo transition and blastocyst development [86]. Also, the levels of Zn^{2+} in the follicular fluid adversely affect the fertilization ability of the human oocyte, and the Cu^{2+} level associates with lower embryo fragmentation [72]. It has been reported that the addition of Cu^{2+} to the IVF medium enhances pronuclear formation but not blastocyst formation [40]. Se^{2+} improves oocyte maturation, fertilization, and blastocyst development in mammals [87], and a low concentration of Ni^{2+} (0.1 mg/L) can lead to increased hormonal sensitivity and maturation activity of frog oocytes [88]. However, there is no study yet on the effects of Ni^{2+} and Se^{2+} on human oocytes.

3. Environmental stressors and human gamete electrophysiology

It seems that ions current occur through CaCC, membrane transporters CHX, NCX, Na^+-dependent Cl^-/HCO_3^- exchanger, NHX, CNG channels, HSper, ROCC, IP3R, CatSper1-4, SLO, KSper, TRP channel, AQP, PMCA, NKX, VGIC (HV, NaV, VGCC, CLC, and KV), Na^+-K^+-ATP_{ase}, K_{ATP}, NKCC, GABA in sperm; and Ca^{2+} uniporter (CU), IP3R, KCa, membrane transporters (CHX, PMCA, Cl^-/OH^- exchanger, NKX, Na^+/NH_4^+ exchanger, NCX, Cl^-/HCO_3^- eDDxchanger, NHX, Na^+/HCO_3^- exchanger, H^+/organic $cation^+$ exchanger, K^+/Mg^{2+} exchanger), swell-activated Cl^- channels, CLC, CaCC, CRAC, Cx, nonselective cation channel, Store-operated STIM-ORAI channels, SOCE, TRP channel, VGIC (VGCC, NaV, HV and KV), K_{ATP}, in the oocyte (Fig. 2) [7,11,14,15,89,90]. Studies demonstrated that some SP and female fluids as well as culture media factors like pHi, Ca^{2+} concentration, xenobiotics, reactive oxygen and nitrogen species (ROS and RNS), temperature, osmolality, and some stimulants, can modulate Ca^{2+} and other ionic concentration that lead to the electrical changes in the cells during fertilization and subsequent embryo development [30]. Components of culture media or buffers for washing and keeping the gametes in *in vitro* condition can affect the electrophysiology of gametes. It seems that the regulation of an extracellular pH of about 7.5 [77], and optimum concentration of extracellular Ca^{2+} in the medium may be useful in improving the ART outcome. A decreased Na^+ concentration in the medium can improve sperm motility and capacitation [91]. Moreover, the solution properties such as temperature, dramatically affect gamete ion channels and protein phosphorylation levels in *in vitro* conditions [32,92]. In some animals, osmolality is one of the major factors altered by K^+ and Ca^{2+} influx and control sperm motility [93]. So, the osmolality of the medium can control the activity of the ionic channels [92]. Contaminants, and drugs like 4-aminopyridine, endothelin-1, endogenous steroids, endocrine disruptors, and plant triterpenoids may have a

critical effect on gamete fertilizing ability via channel selective inhibition [49,59]. Also, electric fields produced by ion channels provide specific signals that regulate many intracellular processes. Although many studies have claimed that low-frequency electromagnetic fields can positively affect sperm and oocyte fertility through this mechanism, it is not clear whether the *in vitro* exposure of gametes to electromagnetic is beneficial or harmful [94]. Moreover, studies showed photocontrol as a valuable optochemical tool that can affect the VGICs in human sperm [95]. Xenobiotics like zinc, tin, and lead compound, phenylurea herbicide, and embryotoxic component which are commonly present in disposable plastic wares used in ART, may affect gametes, embryos, and reproductive processes [96]. However, it was reported that PMCA has a role in eliminating toxic heavy metal ions (*e.g.*, Co^{2+} and Pb^{2+}) [20,38]. As we know, lipids of the gamete membrane and the polarized localized surface antigen migration in maturation processes have a vital role in regulating gamete interactions and stimulating gametes' fertilization ability [97]. Peroxidation of gamete lipids by ROS and RNS may also disrupt all the mentioned gamete functions [98,99]. The Ca^{2+}-dependent NADPH oxidase (NOX5) as a major generator of ROS can couple with Ca^{2+} during sperm activation and disrupt the AR and sperm-oocyte fusion [98,99]. Limitations of oxygen delivery to gamete in culture media and regulation of atmospheric pressure, directly influence the gamete intracellular homeostasis. Studies showed that different spermatozoon–oocyte impact angle (SIA) and friction yield different electrical changes during fertilization because of the local gamete contact stress and ZP deformations in the effect of sperm penetration [100]. However, there is still no consensus on the optimal SIA for sperm penetration. *In vivo*, the endocrine system has been reported to increase intracellular Ca^{2+} through the CatSper mechanism [43,49]. Also, the CCs surrounding the oocyte produce and release progesterone, which exposures human spermatozoa to this stable or gradient progesterone and increases intracellular Ca^{2+} through progesterone-induced Ca^{2+} signaling to prompt spermatozoa to undergo sharp changes which are essential for sperm motility and reorientation [14,36,47,49,101].

CONCLUSIONS

Ionic currents are essential for GVBD, resumption of nuclear maturation in prophase-I and MI-arrested oocytes, and also for interaction of oocyte PM with spermatozoa. Ionic currents play significant roles in sperm production, function, and the initiation of AR, which converts the immature inactive sperm into the fertile one. Following the sperm entry, a species-dependent fertilization current and a large hyperpolarization and depolarization of membrane potential occur in the oocytes. These events coincide with the initiation of embryo development. In this systematic review, studies on the participation of ionic currents in the human gamete physiology and fertilization were discussed. That ionic currents play critical roles from gametogenesis to embryo development like the regulation of sperm motility, sperm reorientation, gamete surface antigen binding during their development, extrusion of the second polar body from the oocyte, gamete fertilizing capability, gamete interactions, the polarized migration of gamete, oocyte-sperm fusion, etc. Since studies are scanty, it encourages more studies to focus on gamete electrophysiology's concept and principles to expand therapeutic approaches to improve *in vitro* maturation, fertilization, and the production of mature gametes in ARTs.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: SD, MD, PS. Data curation: SD, MD. Formal analysis: SD, MD, PS. Investigation: SD, MD. Methodology: PS. Project administration: PS. Resources: SD, MD. Supervision: PS. Visualization: SD, MD, HRKK, PS. Validation: HRKK, PS. Writing – original draft: SD, MD. Writing – review & editing: SD, MD, HRKK, PS.

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